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Highlights

The short- and long-term efficacy of antipsychotic treatment are discussed.

The clinical efficacy of antipsychotics is centered on dopamine D2 receptor blockade.

D2 receptor blockade can lead to multiple outcomes including reduced efficacy, no response and side effects.

Here we consider that post-synaptic D2 receptor blockade is not sufficient for antipsychotic efficacy.

It is suggested that the antipsychotic efficacy can result from the combination of presynaptic D2 autoreceptors reserve activation by the endogenous dopamine and the blockade of postsynaptic dopamine receptors by antipsychotics.

Abstract

All antipsychotics bind to the dopamine D2 receptor. An “optimal” level of D2 receptor blockade with antipsychotics is thought to ameliorate the positive symptoms of schizophrenia. However, persistent D2 receptor blockade is associated with a deteriorating clinical response in a subset of patients. Interestingly, antipsychotics with a weaker D2 receptor binding profile appear somewhat superior in this respect. This evidence challenges the hypothesis that D2 receptor blockade is the sole mechanism of antipsychotic efficacy and points to consistent inter-individual responses to antipsychotic treatment.

Here, we hypothesize that clinically effective doses of antipsychotics would lead to the formation of a D2 receptor “reserve” that is likely composed of presynaptic dopamine D2 autoreceptors. The majority of the remaining postsynaptic dopamine receptors are instead occupied by antipsychotics. Endogenous dopamine would then mainly interact with this D2 autoreceptor reserve, thereby reducing the presynaptic synthesis and release of dopamine and resulting in an indirect antipsychotic effect. This new proposal reconciles conceptual and empirical gaps encountered when clinical outcomes are compared to the pharmacology of antipsychotics.

Dopamine, the antipsychotic molecule: a perspective on mechanisms underlying antipsychotic response variability

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Abstract

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Introduction

Schizophrenia is a severe psychiatric disorder, which has a stark and profound effect on both afflicted individuals and society as a whole (Owen et al., 2016). Genes play a significant role in schizophrenia as they increase the effect size at which environmental risk factors

trigger psychosis in affected patients (van Os et al., 2010). Current genetic data particularly from recent large-scale Genome Wide Association Studies (GWAS) suggest that genes underlying the expression of the core symptoms of schizophrenia are associated with abnormalities in dopaminergic and glutamatergic neurotransmission (Schizophrenia Working Group of the Psychiatric Genomics, 2014) as well as with the overexpression of immune system genes, including those genes regulating synaptic pruning, such as complement C4 (Sekar et al., 2016).

According to the most commonly used diagnostic manuals (DSM-V and ICD10), the core symptoms of schizophrenia include positive and negative symptoms that are significantly co-expressed with cognitive deficits (Joyce and Roiser, 2007). Schizophrenia progresses in a stereotypical manner with mild cognitive and occasional, limited psychotic symptoms (early at-risk phase) preceding the first psychotic episode (late at-risk phase), at which point approximately 40% of patients will transition to chronic psychosis (Fusar-Poli et al., 2013).

The emergence of frank positive symptoms that accompany the onset of psychosis is currently managed clinically through the prescription of antipsychotic drugs (Kapur and Mamo, 2003). While these drugs belong to heterogeneous chemical classes and act on the brain through distinctive mechanisms, they all share in common (albeit with differing affinity) the ability to bind and act at central dopamine D2 receptors. Furthermore, several lines of evidence suggest that this D2 binding property is the key therapeutic mechanism of all current antipsychotics in ameliorating at least the positive symptoms of psychosis. Specifically, this idea is consistent with substantial evidence pointing to disrupted presynaptic dopamine neurotransmission as a hallmark pathological mechanism driving the development of psychotic symptoms (Howes et al., 2012; Howes et al., 2017b). However, although the positive symptoms of psychosis are usually ameliorated in response to first-line antipsychotic treatment, up to 74 % of patients experience a relapse and re-emergence

of positive symptoms (Lieberman et al., 2005). Moreover, there remains a residual group of patients who do not respond to antipsychotic treatment and thus experience long-term positive symptoms without relief. Here, it is important to state clearly that when we refer to antipsychotic treatment response, or clinical efficacy, we are primarily talking about the amelioration of the positive symptoms of schizophrenia. Generally speaking, there is consensus that the negative and cognitive symptoms of schizophrenia are difficult to treat with current antipsychotic medications (although this may not hold true in all cases) and symptoms within these domains are considered to be chronic and enduring, with long-term debilitating effects on social and cognitive functioning (Howes et al., 2017a; Tsapakis et al., 2015).

The causes underlying these clinical limitations are currently not understood, as they appear to be independent of the action of antipsychotic drugs on D2 receptors. It is not the goal of the present work to analyze all issues involved in the treatment of the full spectrum of schizophrenia symptoms. Instead, we will focus on the historical and neurobiological evidence that weakens the assumption that dopamine D2 receptor blockade is the main mechanism of antipsychotic efficacy in the control of positive symptoms. For this reason, we first provide the historical background of the D2 receptor theory of antipsychotic drug action. Second, we then discuss the clinical limitations of this approach and third, we advance a novel and more dynamic hypothesis for the therapeutic mechanism of action of antipsychotic drugs.

A short history of the dopamine D2 receptor theory of antipsychotic drug action

Antipsychotic treatment has significantly contributed to improving the medical and psycho-social wellbeing of patients with schizophrenia over the course of past century. To date,

antipsychotics remain a necessary first-line treatment for the management of the positive symptoms of schizophrenia spectrum and other psychotic disorders.

Before the introduction of antipsychotic agents, the principal pharmacological treatment of psychosis was insulin coma therapy (Ban, 2001; Sakel, 1937). The first pharmacological advancements in treating psychosis were documented by Hamon et al. (Hamon et al., 1952) and subsequently by Delay et al. in 1952 (Delay et al., 1952). These seminal studies demonstrated that the phenothiazine chlorpromazine could alleviate both audiovisual hallucinations and lessen the internal voices reported by schizophrenic patients. This serendipitous discovery, along with the psychopharmacological characterization of reserpine (Barsa and Kline, 1955), was seminal in driving the development of compounds with a similar pharmacological profile (Haase, 1954; Steck, 1954). These include the butyrophenone haloperidol in 1958 (Janssen, 1992), now the classic reference antipsychotic, which displayed both therapeutic efficacy for schizophrenia positive symptoms, but also strong motor side effects, termed extrapyramidal symptoms (EPS). The introduction of the dibenzodiazepine clozapine in 1960 was the first attempt by scientists and clinicians to isolate the therapeutic effects of an antipsychotic medication from these other unwanted (mainly EPS) side effects (Gross and Langner, 1966; Hippius, 1989).

From this point onward, antipsychotic drugs were regularly prescribed in clinical practice to treat schizophrenia and related psychotic disorders, despite the fact that their mechanisms of action were still largely unknown. Indeed, the neurochemical properties of synapses and various brain neurotransmitters had been only just been discovered (for a historical overview we refer the reader to (Ban, 2001)). The dominant thinking in this period was that the efficacy of antipsychotics resulted from their interaction with the serotonin system (Gyermek et al., 1956). This idea, however, was soon displaced by the observations of Carlsson and

Lindqvist in 1963 that both clozapine and haloperidol increased the turnover of catecholamines in the mouse brain, due to catecholamine receptor blockade (Carlsson and Lindqvist, 1963), providing evidence for a neurobiological basis of antipsychotic treatment efficacy. Building on these new discoveries, diverse generations of antipsychotic drugs (i.e. first/second generation, FGA/SGA) were developed using a dopamine agonist-antagonist screening paradigm (Lehmann and Ban, 1997) and made commercially available in the 1970s. Eventually, in a second series of seminal experiments, it was revealed that all antipsychotics share the ability to block the dopamine D2 receptor (Creese et al., 1975; Seeman et al., 1975). Furthermore, their binding affinity for the brain D2 receptor, but not for other receptors, is significantly correlated with their clinical efficacy in alleviating the positive symptoms of schizophrenia (Creese et al., 1976; Seeman and Lee, 1975; Seeman et al., 1976a; Seeman et al., 1976b).

Clinical efficacy of antipsychotics

The efficacy of a pharmacological treatment is substantially based on the resulting response to a given drug at a particular dose. Thus, a pharmacological response can be defined, within a certain extent, as minimal or maximal proportionally to the dose used (i.e. $\log_{10}$ dose). Mechanistically, the response to a drug arises from an interaction between a drug and a molecular target, such as membrane-bound receptors and/or intracellular enzymes, which cause downstream changes in cellular signalling and ultimately lead to a predictable pharmacological response. This apparent linearity in drug-dose response that is potentially achievable in a vitro preparation, is much more complicated to attain in a clinical setting. For example, a therapeutic response to psychiatric drug treatments is complicated to predict as it depends on a balance among the several chemical interactions mentioned before, and the individual genetic and psychosocial factors. Furthermore, the pharmacological treatments used in psychiatry, such as the antipsychotic drugs, act, through different mechanisms (see

Amato 2015 and Amato et al. 2016a for an overview) on multiple classes of neurotransmitter receptors including adrenergic, cholinergic, dopaminergic, histaminergic, and serotoninergic receptors (Lieberman et al., 2008), which altogether contribute to decrease the predictability of the response to antipsychotics. Despite this heterogeneity, dopamine D2 receptors are however considered the primary target for the ameliorative effects of antipsychotics on positive psychotic symptoms (Kapur and Mamo, 2003; Miyamoto et al., 2005).

Accordingly, antipsychotics appear to be ineffective in the absence of dopamine D2 antagonism (Johnstone et al., 1978). This is true for antagonism of both the high- and low-affinity functional states of the D2 receptor (Graff-Guerrero et al., 2009a). Clinical efficacy of antipsychotics also varies with both the binding affinity of a given antipsychotic to the D2 receptor, as well as the degree of receptor occupancy achieved following a single dose (Farde et al., 1992; Kapur et al., 2000a; Knable et al., 1997). In addition, antipsychotic drug efficacy is also related to the dissociation constant of the drug from the D2 receptor (Kapur and Seeman, 2000; Kapur and Seeman, 2001). For example, haloperidol and chlorpromazine show high binding affinity towards D2 receptors (Creese et al., 1976; Seeman and Lee, 1975) and are clinically effective when approximately 60-80% of central D2 receptors, are occupied by these drugs, which is now defined as the “antipsychotic therapeutic window” (Farde et al., 1992; Kapur et al., 2000a; Knable et al., 1997; Nordstrom et al., 1993). Haloperidol and chlorpromazine once bound, also dissociate slowly from central D2 receptors (Kapur and Seeman, 2001). In contrast, newer antipsychotics such as risperidone, olanzapine and particularly clozapine, show the opposite pharmacological profile. They have low binding affinity for D2 receptors (Creese et al., 1976; Seeman and Lee, 1975; Seeman et al., 1976b) and are clinically effective at a lower level of D2 receptor occupancy (less than 50-60% on average) (Farde et al., 1992; Kapur et al., 1998; Kapur et al., 1999; Kapur et al., 2000b; Scherer et al., 1994). These drugs, once bound, also dissociate rapidly from central D2 receptors (Kapur and Seeman, 2000; Kapur and Seeman,

2001; Seeman and Tallerico, 1998; Seeman and Tallerico, 1999). These diverse profiles of action at central D2 receptors but also interactions with other neurotransmitter receptors (i.e. adrenergic, serotoninergic etc.) combine to define the specific efficacy profile of individual antipsychotic drugs. Thus, clinical practice counterbalances the unique pharmacology of antipsychotics by using strategies such as differential dosing and treatment duration with a defined drug, followed by switching or combining with other antipsychotic drugs (Buckley and Correll, 2008; Galling et al., 2017). For example, at low doses haloperidol and chlorpromazine yield a larger D2 receptor occupancy (Kapur et al., 1996) as compared to risperidone or other newer antipsychotics, which must be administered at higher doses to reach a similar receptor occupancy (Kapur and Seeman, 2001), a strategy that works in a small proportion of patients (see concerns #4 and #5 below). Furthermore, it is now clear that all currently available antipsychotics differ more in respect to their side-effect profiles, whilst clinical efficacy on positive symptoms varies less between FGA (e.g. haloperidol) and SGA (e.g. olanzapine) (Fleischhacker et al., 2014; Leucht et al., 2013; Miyamoto et al., 2005). Importantly, a very high clinical heterogeneity and inter-individual therapeutic variability is evident following antipsychotic drug treatment (Gilbert et al., 2014; Insel and Cuthbert, 2015; Levine et al., 2012). These pitfalls of antipsychotic treatment will be described in more detail in the next section.

Clinical failure of antipsychotics: Ten reasons to look beyond blockade of D2 receptors in the search for new antipsychotic drugs

Based on the aforementioned lines of evidence described in the preceding sections, the blockade of central dopamine D2 receptors remains a reference point for the incremental development of “new” antipsychotic drugs. However, despite the obvious advantages brought by the therapeutic use of antipsychotics, several lines of research highlight the

extreme inconsistency of this class of drugs in relation to both clinical and preclinical outcomes. The following are what we consider to be the most common concerns, based on the extant literature and our own lines of scientific research:

1) Antipsychotic efficacy decreases with time despite sufficient D2 receptor blockade

In clinical trials, positive symptoms of individuals with schizophrenia generally improves initially with antipsychotic drug treatment. However, a large proportion of subjects drop out of treatment altogether at around the third month of treatment and sometimes earlier (McCue et al., 2006; McEvoy et al., 2006; Stroup et al., 2006). This is, at least in part, due to decreasing efficacy of the drug in relieving positive psychotic symptoms (Lieberman et al., 2005). Importantly, patients with schizophrenia may also experience a relapse of positive symptoms despite receiving antipsychotic drug treatment (Emsley et al., 2013; Kishimoto et al., 2014; Leucht et al., 2012; Lieberman et al., 2005; McCue et al., 2006; McEvoy et al., 2006; Nielsen et al., 2015; Stroup et al., 2006). This occurs with no overall appreciable differences between FGA and SGA (Jones et al., 2006; Lieberman et al., 2003; Lieberman et al., 2005; McCue et al., 2006; McEvoy et al., 2006; Stroup et al., 2006), although clozapine is a notable exception (Leucht et al., 2013; McEvoy et al., 2006). Strikingly, such relapses occur despite sufficient central dopamine D2 receptor occupancy, as defined by the antipsychotic therapeutic window (60-80%) (Remington et al., 2006; Uchida and Suzuki, 2014).

2) Long-term D2 receptor blockade produces counter-therapeutic effects such as dopamine supersensitivity psychosis

The sustained blockade of central dopamine D2 receptors that occurs with chronic antipsychotic drug treatment has been shown, paradoxically, in at least some cases, to

result in psychosis itself, through the induction of a compensatory dopamine supersensitivity, known as dopamine supersensitivity psychosis (DSP) (Chouinard et al., 1978). Clinically, DSP is characterized by withdrawal psychosis, tolerance to antipsychotic effects, *de novo* psychotic symptoms and the development of tardive dyskinesia (TD) (Chouinard and Jones, 1980). DSP is thought to underlie relapse in roughly 40% of treated schizophrenia patients (Fallon et al., 2012). Notably, DSP can also occur due to sustained prescription of high doses of antipsychotics (Chouinard et al., 1982) or long-term treatment with FGA (Chouinard and Jones, 1980; Jenner et al., 1983). In contrast, it occurs less commonly following long periods of treatment with SGA that have lower D2 affinity as compared to FGA, such as clozapine (Ekblom et al., 1984; Li et al., 2009; Rupniak et al., 1984; Rupniak et al., 1985; Seeman et al., 2005), olanzapine (Bedard et al., 2013; Dias et al., 2013; El Hage et al., 2015; Llorca et al., 2001) or with partial D2 receptor agonists such as aripiprazole (Tadokoro et al., 2012; Varela et al., 2014). The SGA risperidone long-acting injectable (RLAI) was found to be effective, and well-tolerated against positive and negative symptoms (Kane et al., 2003) with higher therapeutic benefits in patients with DSP switched to RLAI (Kimura et al., 2014). This beneficial effect of RLAI, especially in DSP patients, is attributed to the longer half-life of the treatment, which stabilizes post-synaptic D2 blockade, thus preventing endogenous dopamine from binding the upregulated $D2^{High}$ affinity receptors (Iyo et al., 2013)

3) Temporally shorter D2 receptor blockade yields improved therapeutic outcomes

Intriguingly, transient D2 receptor blockade renders antipsychotics with this property both safer and somewhat more clinically effective than antipsychotic drugs with a longer duration of D2 receptor blockade (Kapur et al., 2000b; Seeman and Tallerico, 1998). As already stated, antipsychotics such as haloperidol that elicit severe EPS bind central D2 receptors

with high affinity and dissociate more slowly than antipsychotics lacking this side effect (Seeman and Tallerico, 1998). This notion is consistent with the fact that SGA dissociate faster from D2 receptors than FGA and further supported by the lower incidence of EPS in patients prescribed SGA (Kapur and Seeman, 2000).

4) The clinical efficacy of antipsychotics and D2 receptor blockade are temporally desynchronized

Antipsychotic efficacy and failure is temporally dissociated from the on- and off- binding kinetics at central D2 receptors. A clinically-effective occupancy of central D2 receptors is achieved ~2-3 hours after drug administration (Takano et al., 2004) and a consistent clinical response may be observed in the first 24 hours and 7 days or more thereafter (Agid et al., 2003; Emsley et al., 2006; Kapur et al., 2000a; Kapur et al., 2005; Leucht et al., 2005; Nordstrom et al., 1992) according to previous studies (Johnstone et al., 1978; Lieberman et al., 1993). Similar temporal dissociations are observed between antipsychotic brain action and treatment failure. As observed above (see Concern #1), patients with schizophrenia may experience a relapse of positive symptoms despite receiving therapeutic doses of antipsychotics that achieve a sufficient central D2 receptor blockade for effective antipsychotic action on positive psychotic symptoms (Emsley et al., 2013; Kishimoto et al., 2014; Leucht et al., 2012; Lieberman et al., 2005; McCue et al., 2006; McEvoy et al., 2006; Nielsen et al., 2015; Stroup et al., 2006). On the other hand, it has also been observed that either relapse in chronically ill schizophrenia patients or the stimulatory effects of apomorphine in rats may not occur for weeks or months after administration of antipsychotics (even after a single dose) is ceased (Campbell and Baldessarini, 1985; Campbell et al., 1985; Cohen et al., 1988; Cohen et al., 1992; Kornhuber et al., 1999; Nyberg et al., 1997). It has also been reported that in conditions of full pharmacological response, D2 receptor occupancy declines in days, while the rate of relapse extends for months (Baron

et al., 1989; Cohen et al., 1992; Kapur et al., 2000a; Viguera et al., 1997). I think you need a closing sentence here?

5) A significant proportion of patients do not respond to antipsychotic drug administration despite achievement of sufficient central D2 receptor blockade

About 20-30% of patients with schizophrenia never show a positive treatment response despite receiving chronic treatment with a dose of an antipsychotic that achieves the critical therapeutic window of central D2 receptor occupancy (Pilowsky et al., 1992; Pilowsky et al., 1993; Wolkin et al., 1989). Patients in this subgroup are defined as resistant to treatment when they 1) have received a validated diagnosis of schizophrenia; 2) receive adequate pharmacological treatment; and 3) exhibit persistent symptoms despite treatment (Howes et al., 2017a). Specifically, treatment resistance is characterized by positive psychotic symptoms that do not improve after three or more periods of treatment, each lasting four to six weeks, with antipsychotics from two or more chemical classes within a timespan of five years (Conley and Kelly, 2001; Kane et al., 1988). While the lack of response to D2 receptor blockade may be consequent to maladaptations interesting substrates other than the dopamine system (Demjaha et al., 2014), it remains puzzling that this may occur despite the strong contingency between dopamine system, psychosis (Howes et al., 2009) and treatment response (Kapur et al., 2000a).

6) Lower affinity blockade of D2 receptors translates into higher antipsychotic efficacy

Clozapine, a compound with low affinity for the D2 receptor, but with potential life-threatening side effects, is a more effective antipsychotic (Leucht et al., 2013) with longer-term efficacy (McEvoy et al., 2006) as compared to antipsychotic drugs with higher affinity for D2 receptors. Clozapine is also therapeutically effective in treatment-resistant patients

(Pilowsky et al., 1992; Wahlbeck et al., 2000). However, our neurobiological understanding of the superior efficacy of clozapine remains unclear.

7) Newer antipsychotics are effective at higher D2 receptor occupancy

The so-called third-generation antipsychotics (i.e. aripiprazole and it's more recent derivative brexpiprazole) still have very high affinity for D2 receptors (Miyamoto et al., 2005), but these drugs are not D2 receptor blockers *per se* (Mailman and Murthy, 2010). These drugs are also effective at higher D2 receptor occupancy, when compared to FGA, in animal models (Natesan et al., 2006). Aripiprazole has a distinctive pharmacologic profile compared to FGA and SGA. Specifically, it displays both agonist and antagonist properties at several G-protein coupled receptors (i.e. agonist at dopamine D2 and 5-HT1A and antagonist at 5-HT2A receptors). Because of this pharmacological profile, aripiprazole is defined as a partial agonist (McGavin and Goa, 2002). It is suggested that the therapeutic effects of aripiprazole are due to a reduction of dopamine release via presynaptic agonism coupled with functional antagonism of postsynaptic D2 receptors (Kikuchi et al., 1995). Interestingly, clinical trials indicate that both aripiprazole and brexpiprazole are effective in treating both positive and negative symptoms of schizophrenia (Mailman and Murthy, 2010).

8) Augmentation is used to counteract antipsychotic failure

It is a common clinical practice to co-administer drugs that increase monoamine levels (i.e. antidepressants) to enhance the overall antipsychotic efficacy in treatment-resistant patients (Mao and Zhang, 2015) (and personal communication with practicing psychiatrists). Specifically, augmentation with antidepressants has been shown to improve the efficacy of antipsychotics for positive (Joffe et al., 2009; Terevnikov et al., 2010; Terevnikov et al., 2011), negative (Raedler et al., 2004; Singh et al., 2010) and cognitive symptoms (Stenberg et al., 2010; Vernon et al., 2014). Although a double blind placebo-controlled study could

not confirm these effects (Usall et al., 2014), observations linking the beneficial effects of monoamine releasers co-administered with antipsychotics are largely in line with data obtained using animal models (Bjorkholm et al., 2015; Marcus et al., 2010; Marcus et al., 2012).

9) Higher dopamine levels in the striatum improve antipsychotic response

Antipsychotics are effective in the presence of moderately high levels of presynaptic dopamine synthesis capacity (Demjaha et al., 2012) and extracellular dopamine in both humans (Abi-Dargham et al., 2000; Roberts et al., 2009; Yoshimura et al., 2003) and rodents (Amato et al., 2011b; Samaha et al., 2007). Furthermore, it was recently suggested that differences in basal dopamine levels (i.e. high vs. low dopamine) may underlie two different schizophrenia subtypes. The high-dopamine type would be more likely to respond to antipsychotic treatments (Howes and Kapur, 2014), in keeping with previous preclinical observations (Amato et al., 2011b; Samaha et al., 2007). In contrast, the low dopamine subgroup would be less likely to respond to antipsychotic treatment.

10) Effects of placebo demonstrate the inadequacy of D2 receptor blockade

Antipsychotics are more effective than placebo for the treatment of the positive symptoms of schizophrenia (Leucht et al., 2013). However, a placebo effect in patients with schizophrenia might be a confounding factor in clinical trials as it can reproduce antipsychotic effects (Kemp et al., 2010), a finding attributed to both patient characteristics and the design of clinical trials of antipsychotics (Agid et al., 2013). Moreover, research has shown that the placebo effect is a genuine psychobiological event (Finniss et al., 2010) driven by different pathways including the μ-opioid receptors (Wager et al., 2007; Zhang et al., 2013; Zubieta et al., 2005), CB1 cannabinoid receptors (Benedetti et al., 2011) and the D2/3 receptors (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez et al., 2002;

Lidstone et al., 2010; Scott et al., 2007; Scott et al., 2008), all underlying positive expectation and learning (Carlino et al., 2016).

Dopamine has been described as guiding placebo responses in pain and Parkinson's disease through the activation of reward mechanisms (Carlino et al., 2016). In placebo analgesia, an increase in dopamine binding to D2/D3 receptors and in opioid binding to μ-opioid receptors occurs in the nucleus accumbens, whereas the opposite occurs during hyperalgesia (Scott et al., 2007; Scott et al., 2008). In a similar fashion, the administration of placebo to patients with Parkinson's disease leads to an increase in extracellular dopamine concentration of about 200% in both nucleus accumbens and dorsal striatum (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez et al., 2002; Lidstone et al., 2010). This effect has been compared to the response to amphetamine in a subject with a functional intact dopamine system (Carlino et al., 2016). It is therefore plausible, that the placebo response in schizophrenia could be mediated to a certain extent by the brain's reward system via stimulation of D2/3 receptors.

Summarizing the ten points above, it follows that significant D2 antagonism can be associated with lack of treatment response, or with efficacy that decays over time, leading to worsening of positive symptomatology and/or in the presence of severe treatment side effects. In contrast, high extracellular dopamine levels or partial stimulation of D2/3 receptors results in higher therapeutic efficacy. Because of this clinical heterogeneity and high therapeutic variability, clinical guidelines strongly recommend adapting treatments to each individual case (Hasan et al., 2013).

Aside from the emergence of DSP that may or may not occur during treatment with antipsychotics (Iyo et al., 2013), to date, there are no mechanistic hints as to why the effects of antipsychotic drugs have such unpredictable variability in their clinical effects in

schizophrenic patients. Nor is it understood why some patients are resistant to antipsychotic treatment, although, one parsimonious explanation for this is the notion that the psychotic symptoms experienced by treatment resistant patients are due to differential neurobiological mechanism, which specifically does not involve sub-cortical hyperdopaminergia (Egerton et al., 2013; Kim et al., 2016). Nevertheless, these phenomena raise the question as to why the blockade of D2 receptors by antipsychotics, which effectively prevents hyperactive dopamine signalling, would produce multiple clinical outcomes in patients, for which there is currently no satisfactory neurobiological explanation. Discussing these important clinical issues by taking into account the complexity of dopaminergic signalling has the potential to help reduce the unpredictability of current therapeutic effects. Ultimately, this would eliminate the still empirical practice of successively trying different antipsychotic drug doses, combinations or augmentation strategies for perhaps months or even years until a clinically "acceptable" treatment response is achieved. In line with this aim, we first summarize the genetic mechanisms underlying pharmacological response variability, gradually narrowing our focus on the complex organization of the neurons that express dopamine receptors. We then explore putative possibilities as to how the complex dopaminergic system may produce diverse therapeutic outcomes after exposure to antipsychotic treatment.

Mechanistic hypotheses for antipsychotic response variability and discrepancies in clinical efficacy and/or treatment response

Genetics

As already suggested, the causes of heterogeneous therapeutic responses to antipsychotics in schizophrenia are likely related to the heterogeneous disease neurobiology amongst patients, which is driven by complex interactions between genetic and a myriad of environmental risk factors for schizophrenia. From a pharmacogenomics point of view,

genetic variants are thought to determine much of the variability in drug response via several pathways. For example, genetic variation can lead to variability in drug action via modification of the mechanisms underlying drug metabolism (pharmacokinetics). For example, genetic variants can affect drug action and elimination affecting the margin between the dosages that are required for efficacy, and those that are associated with serious toxicity.

An alternative mode through which genetic variants can affect drug response is via pharmacodynamic mechanisms, which refers to the relationship between the drug concentration and its effect. As a result, individuals with identical plasma and tissue drug concentrations vary in their behavioural and cognitive responses. Thus, drug effects can be variable because the specific molecular target on which the drug acts varies within a population (often genetically determined). A more generic form of pharmacodynamic variability is the variability of the broader biological context that affects the expression of tens or hundreds of genes mediating the interaction between a drug and its target molecules. (Roden and George, 2002). Thus, for a given antipsychotic treatment, individual responses might well be expected to be somewhat variable (Kapur et al., 2000a; Levine and Rabinowitz, 2010; Pilowsky et al., 1992) despite similar degrees of central D2 receptor occupancy (Wolkin et al., 1989). Similarly, side effects may also vary among patients despite similar levels of central D2 receptor occupancy (Kapur et al., 1995; Seeman and Tallerico, 1998) and may even occur at low occupancy levels (Melkersson et al., 2001). Generally, this complex drug-response scenario is interpreted as an inherited pharmacological response (Arranz and de Leon, 2007) and/or as a consequence of an individual's basal dopaminergic levels (Laruelle et al., 1996). For example, differences in basal dopamine (i.e. high vs. low dopamine) may underlie different schizophrenia subtypes, as was recently

suggested using animal models of prodromal schizophrenia (Amato et al., 2016b) or human patients (Howes and Kapur, 2014). Of course, individual differences in basal dopamine are also likely to depend on the genetic background of the individual. In agreement with this is the consistent, albeit preliminary evidence, that different therapeutic responses to antipsychotics such as clozapine, aripiprazole and risperidone might be related to genetic variation in D2 receptors (Blasi et al., 2015; Huang et al., 2016; Lencz et al., 2006; Schafer et al., 2001; Zahari et al., 2011; Zhang et al., 2015). This is true not only for therapeutic effects, but also in relationship to side effects. For example, a recent meta-analysis demonstrated that antipsychotic-related weight gain is dependent on specific genetic variants, with polymorphisms in D2 receptors having one of the largest effect sizes (Zhang et al., 2016). Furthermore, pharmacogenetic interactions for antipsychotic therapeutic and adverse effects have been suggested for other dopamine related genes such as D1, D3, D4, COMT or DAT (Arranz and de Leon, 2007; Lerer et al., 2002; Papaleo et al., 2012; Potkin et al., 2003; Reynolds et al., 2005; Zalsman et al., 2003; Zivkovic et al., 2013). From preclinical studies, genetic variation in all these genes may be expected to modulate basal dopamine levels in the brain (Giros et al., 1996; Papaleo et al., 2008; Usiello et al., 2000). Despite this, the mechanisms underlying these pharmacogenetic interactions and the functional importance of the identified dopamine-related genetic polymorphisms in humans are still unknown and require specific assessment. The pharmacogenomics field in the context of psychiatric disorders is still at an early stage in its evolution. However, increasing evidence suggests optimizing treatment based on individual's genetic architecture might be a promising future direction to improve the efficacy and use of antipsychotics. Cheap and reliable genetic screens to stratify patients could help direct interventions for "responders" or aid in the development of new targets for "non-responders".

Dopamine receptors

Another potential source of response variability to antipsychotic treatment may arise from differences in the distinct types of dopamine receptors.

There are two types of receptors that mediate dopamine neurotransmission: D1-like receptors (which include the D1 and D5 receptors) and the D2-like receptors (which include the D2, D3 and D4 receptors) (Ballesteros et al., 2001; Coley et al., 2000). Both D1- and D2-like receptors share a common seven transmembrane domain structure with an extracellular amino terminus and an intracellular carboxyl terminus. The intracellular carboxyl terminus is approximately seven times longer in D1-like receptors than in D2-like receptors and it is richer in specific monoacid residues, such as serine and threonine.
Functionally, the mechanism of signal transduction following binding and activation of D1- and D2-like receptors by dopamine is mediated through different second messenger G-protein subtypes (G_{α}, G_{β}, and $G_{\gamma)}$, which initiate an intracellular second messenger cascade leading to adenylyl cyclase (AC) activation or inhibition. The stimulation of D1-like receptors activates AC and facilitates neuronal excitability by the potentiation of inward Na^{+} currents through N-methyl-D-aspartate (NMDA) receptors, along with activation of both calcium and sodium membrane-bound ion channels (Surmeier et al., 2010). In contrast, stimulation of D2-like receptors inhibits AC, facilitating neuronal hypoactivity through the closure of membrane-bound calcium channels and hyperpolarsation via activation of inwardly rectifying potassium channels (Beaulieu and Gainetdinov, 2011). Interestingly, both D1 and D2 receptors are found in two inter-convertible states exhibiting either high or low agonist affinity (Richfield et al., 1989; Seeman et al., 1985). The high affinity state has, as the name suggests, a high affinity for dopamine and is coupled with a G-protein messenger that works as a mediator of the functional effects of dopamine. The low affinity state instead has low affinity for dopamine and is uncoupled from the G-protein, making the receptor functionally inert (Seeman, 2008). Similar functional differentiation is found in D3 receptors, although

this characteristic appears more controversial (Graff-Guerrero et al., 2009b). Furthermore, dopamine has higher affinity for D2 than for D1 receptors, regardless of functional state (Marcellino et al., 2012).

Dopamine receptors display an additional functional heterogeneity through the fact that D1 and D2 receptors may work as either autoreceptors or heteroreceptors. These terms primarily refer to whether the receptor proteins are localised or clustered on either the soma or axon terminals of dopaminergic (autoreceptors) or non-dopaminergic (hetero-receptors) neurons (Feuerstein, 2008). Critically, depending on their location, dopamine receptors mediate different physiological activities in response to agonists or antagonists. For example, D2 autoreceptors expressed on the soma and presynaptic axon terminals of dopaminergic neurons modulate the synthesis, release and uptake of dopamine (Missale et al., 1998) as well as the co-release of neurotensin (Bean et al., 1990; Bean and Roth, 1991). Heteroreceptors, which include both D1 and D2 receptors, are also found in non-dopaminergic neurons and their activation or inactivation can affect the release of monoamines as well as GABA, glutamate and acetylcholine (Feuerstein, 2008). The complex organization underlying dopamine neurotransmission raises the legitimate question as to whether blockade of D2 receptors may lead to multiple potential outcomes depending on the relative weights of pharmacological activity of D2 receptors on disparate populations of neurons releasing various neurotransmitters.

An additional level of complexity arises from the fact that multiple isoforms of dopamine receptors exist. Accordingly, the D1-like receptors are encoded by genes with a single exon (intronless), which do not generate multiple variants of the receptors. In contrast, the D2-like receptors are encoded by intron-containing genes, thus leading to production of alternatively spliced transcripts (Dal Toso et al., 1989; Giros et al., 1989; Griffon et al., 1996; Lichter et

al., 1993; Monsma et al., 1989; Van Tol et al., 1992). Spliced isoforms of the dopamine D2 receptors have distinct physiological properties and cellular localizations. For example, the D2 short (D2S) isoform plays an autoreceptor role and is relatively more abundant in the substantia nigra and in the hypothalamus (Guivarc'h et al., 1995). In contrast, the D2 long (D2L) isoform has been found to be expressed primarily post-synaptically (De Mei et al., 2009; Usiello et al., 2000). Thus, the different physiological roles of pre- and post-synaptic D2 receptors may account for the potentially different antipsychotic outcomes (treatment efficacy, failure and non-response). These issues will be discussed in depth in the next sections.

Circuitry of D1 and D2 receptor-expressing neurons

As mentioned in the previous section, dopamine receptors may be found on both dopaminergic and non-dopaminergic neurons, increasing response heterogeneity to agonists and antagonists and consequently to antipsychotic treatment. This complex organization allows dopamine neurotransmission to serve as the communication core of the basal ganglia (BG) network.

The BG includes several nuclei that work together to produce appropriate goal-directed behaviours (action selection), to correctly evaluate different aspects of reward, including value versus risk and predictability, and to inhibit maladaptive choices based on previous experience (Haber, 2014). These calculations rely on the integration of input and output neurotransmission signalling that converges into the striatum from numerous cortical and subcortical brain areas. Within this circuitry, dopamine receptor-expressing neurons play a central role in regulating reward, cognition, and motor activity and subpopulations of these neurons serve different functions (Heinsbroek et al., 2017).

The majority of the D1 and D2 receptor-expressing neurons are located in the striatum and are predominantly GABAergic medium spiny neurons (MSNs, 90-95% of striatal neurons)

with the remainder characterized as cholinergic or GABAergic interneurons. MSNs also co-express substance P, dynorphin and M4 cholinergic receptors along with D1 receptors. MSNs expressing D2 receptors also express enkephalin, neurotensin and A2a adenosine receptors (Beaulieu and Gainetdinov, 2011; Scofield et al., 2016).

The striatum is the main input nucleus of the BG and receives topographically organized projections from the cerebral cortex, the thalamus, the substantia nigra (SN) and the ventral tegmental area (VTA). Cortical and thalamic afferent projections from excitatory pyramidal neurons use glutamate as a neurotransmitter, while projections from SN and VTA are dopaminergic (Haber, 2014). In turn, the striatum sends MSN axonal projections to the output nuclei of the basal ganglia, the substantia nigra, via the striatonigral pathway (or direct pathway), and the external segment of the globus pallidus (GPe; striatopallidal pathway or indirect pathway) (Haber, 2014). These two distinct pathways have opposing functional roles in regulating motor activity, with the direct pathway generally serving to facilitate behaviour and the indirect pathway inhibiting it (Lobo and Nestler, 2011). However, evidence emerging from the application of recent technologies, combining genetics, optics, electrophysiology and fluorescence microscopy reveals that striatal innervation of the output nuclei includes mixed D1- and D2- MSN projections (Cazorla et al., 2014; Kupchik et al., 2015; Saunders et al., 2015). This raises the possibility that regulation of behaviour by MSNs and the effects of drugs acting on these receptors may involve complex overlapping innervations.

If we assume that antipsychotics work mainly by blocking dopamine D2 receptors, then the next logical question to ask is which of the many D2 receptors is the target of antipsychotic drugs? Moreover, which type mediates the beneficial therapeutic effects and which the adverse side effects? In fact, D2 receptors imbedded in the membrane of heterogeneous

neurons can produce diverse physiological responses. It is likely that the discovery of the precise D2-pathway recruited by antipsychotics would help to overcome the ten clinical issues observed previously. However, it is not the aim of the present review article to discuss the many D2 receptor-mediated mechanisms leading to multiple clinical outcomes. Instead, in the following section, we will focus on one potential, tractable role played by presynaptic D2 receptors in mediating antipsychotic effects.

Time course of antipsychotic efficacy or failure and D2 receptor occupancy

An additional source of variability during treatment with antipsychotics relates to the time interval between drug action and the therapeutic response, to which we have referred to previously (see concern #4 above). The extant literature points to a therapeutic antipsychotic response after a delayed period of roughly 2-3 weeks treatment (Johnstone et al., 1978; Lieberman et al., 1993). In contrast, a steady state level of receptor occupancy by antipsychotics is achieved within a few days following treatment initiation (Kapur et al., 2000a; Nordstrom et al., 1992). The current interpretation of this temporal gap between achieving steady state D2 receptor occupancy and clinical efficacy is that the continued administration of antipsychotics for at least two weeks inactivates firing activity of ventral mesencephalic dopaminergic neurons in the brain, particularly in the VTA. This "depolarization block" hypothesis implies that VTA DA neurons become inactive after 3 weeks of exposure to antipsychotics, based on electrophysiological recordings in rodents (Grace and Bunney, 1984; Grace, 1992; Lane and Blaha, 1987). However, the role of this mechanism in antipsychotic efficacy has never been clearly confirmed either clinically or pre-clinically in anesthesia-free animals using a clinically-relevant dose and route of administration of an antipsychotic (Klitenick et al., 1996; Mereu et al., 1994; Mereu et al., 1995; Moghaddam and Bunney, 1993).

Importantly, more recent studies have clarified that the temporal delay between antipsychotic treatment initiation and clinical response may be better interpreted as a delay preceding the realization of the full therapeutic benefit, rather than a delayed effect onset (Agid et al., 2003; Leucht et al., 2005). This hypothesis receives mechanistic support from the finding that many antipsychotics progressively accumulate in the brain following chronic treatment (Cohen et al., 1988; Cohen et al., 1992; Kornhuber et al., 1999; Korpi et al., 1984; Tsuneizumi et al., 1992). This is principally a consequence of their weak base chemical structure, which allows them to accumulate in intracellular compartments (Rayport and Sulzer, 1995) such as endosomes and synaptic vesicles in pre-synaptic nerve terminals (Tischbirek et al., 2012). Accordingly, we have previously observed that the accumulation of antipsychotics into synaptic vesicles creates an “antipsychotic reservoir” that is co-released from pre-synaptic nerve terminals upon stimulation, along with endogenous dopamine, which triggers auto-inhibition of neurotransmitter release. Thus, the release of nanomolar concentrations of antipsychotics inhibits presynaptic voltage gated sodium channels, which leads to reduced presynaptic calcium influx and reduces dopamine neurotransmission (Tischbirek et al., 2012).

Although this mechanism offers a neurobiological interpretation for the slow development of a full antipsychotic response, it does not explain the early beneficial therapeutic effects of antipsychotics observed in humans (Kapur et al., 2005) or in laboratory animals on behavioural tasks with dimensional relevance to psychosis such as pre pulse inhibition of the startle response or amphetamine-induced hyperlocomotion (Li et al., 2007). Also, it does not take into account the gradual loss of efficacy that develops over time (see concern #4 above). This gradual loss of antipsychotic efficacy and the occurrence of relapse are often attributed to dopamine supersensitivity (Chouinard et al., 1978; Emsley et al., 2013; Iyo et al., 2013; Tarsy and Baldessarini, 1974). A similar scenario is observed in preclinical

research. Animal models adopting clinically-relevant doses and pharmacokinetics of antipsychotic exposure (Tauscher and Kapur, 2001; Wadenberg et al., 2001) have shown that antipsychotic efficacy decreases as a function of the duration of exposure (Amato et al., 2011b; Andersen and Pouzet, 2001; Martinez et al., 2000; Samaha et al., 2007). This effect is also interpreted in terms of dopamine supersensitivity (Samaha et al., 2007). It is suggested that DSP and TD are caused by an up-regulation of striatal D2 receptors leading to an enhanced dopamine-based activity in humans (Kornhuber et al., 1989; Mackay et al., 1982; Silvestri et al., 2000) and animal models (Jenner et al., 1982; Samaha et al., 2007; Seeman et al., 2005; Tarsy and Baldessarini, 1974) that show vacuous chewing movements (VCM) an accepted rodent proxy for TD symptoms (Turrone et al., 2003a; Turrone et al., 2003b; Turrone et al., 2005). However, changes in D2 receptor density have not been observed in all patients previously exposed to antipsychotics (Davis et al., 1991; Laruelle, 1998) and therefore the question of whether there is one precise mechanism mediating both the onset and offset of the antipsychotic response remains to be determined. Here, we make an attempt to address this question by looking at the effects of antipsychotics on levels of endogenous dopamine in the brain.

Dopamine, the antipsychotic molecule

While it makes sense that antipsychotics are more effective in the presence of high extracellular dopamine, due to its association with psychoses, it is less clear why this happens only initially, but not over time in the context of longer treatment regimens. This raises obvious questions about the neurobiological condition of schizophrenia patients during initial and chronic phases of treatment with antipsychotics. Does dopamine play a role initially, but not chronically? Microdialysis studies have consistently shown that acute exposure to any antipsychotic leads to increased extracellular levels of dopamine and its metabolites in the cortico-striatal pathway of rodents (Chen et al., 1992; Ichikawa and

Meltzer, 1991; Imperato and Di Chiara, 1985; Meltzer et al., 1994; Tanda et al., 2015; Westerink et al., 1989; Zetterstrom et al., 1984). This effect lasts approximately 7 days in naïve rats following exposure to clinically relevant antipsychotic doses that mimick human pharmacokinetics (Amato et al., 2011b; Samaha et al., 2007). On the other hand, the extracellular levels of cortico-striatal dopamine are markedly reduced upon further chronic exposure (>7 days) to the same antipsychotics, at the same dose. Thus, compared to acute exposure, chronic antipsychotic exposure decreases (or produces no changes in) dopamine and its metabolites (Chen et al., 1991; Chen et al., 1992; Hernandez and Hoebel, 1989; Hernandez et al., 1990; Ichikawa and Meltzer, 1991; Invernizzi et al., 1995). Recent studies have shown that this effect occurs as early as the second week of exposure in naïve rats receiving clinically relevant antipsychotic doses (Amato et al., 2011b; Samaha et al., 2007). Preclinical models have also shown that antipsychotics are effective at the same D2 occupancy observed in human conditions (60-80% (Wadenberg et al., 2001)) and, similar to what is seen in humans, antipsychotic efficacy decreases over time. Specifically, antipsychotic efficacy lasts about one week in animal models, reversing both the pre-pulse inhibition deficit and hyperlocomotor activity in response to pharmacological and non-pharmacological challenge in naïve rats (Amato et al., 2011b; Andersen and Pouzet, 2001; Martinez et al., 2000; Samaha et al., 2007). This efficacy significantly decreases thereafter, coupled with the emergence of vacuous chewing movements (VCM), the aforementioned rodent proxy of TD (Amato et al., 2011b; Andersen and Pouzet, 2001; Martinez et al., 2000; Samaha et al., 2007). Thus, the time-related decay of efficacy and emergence of adverse side-effects of antipsychotics in preclinical models resembles that observed in humans (Lieberman et al., 2003; Lieberman et al., 2005; McCue et al., 2006; McEvoy et al., 2006; Stroup et al., 2006). Strikingly, the time-course of antipsychotic failure in rodent models is directly comparable to the time-course of changes in extracellular levels of cortico-striatal

dopamine induced by the same antipsychotics under the same conditions (Amato et al., 2011b; Samaha et al., 2007).

This raises the question as to whether this increase in extracellular dopamine has any potential pharmacological significance for antipsychotic efficacy in rodent models. In drug-naïve rats, extracellular dopamine is cleared from the synapse within milliseconds following its release (Garris et al., 1994; Wightman et al., 1988). In contrast, following chronic exposure to clinically-relevant doses of antipsychotics, high basal dopamine levels may be recorded for up to 7 days (Amato et al., 2011b; Samaha et al., 2007). It may therefore be suggested that the prolonged high extracellular dopamine levels driven by antipsychotic exposure bind to a "reserve" of central D2 receptors, which can be derived by subtracting the efficacy-based D2 receptor occupancy (60-80%) from the total available D2 receptor pool (100%). This would result in about 40-20% of D2 receptors forming a "reserve", which would be available for binding by endogenous dopamine. But what is the nature of these D2 receptors?

As described already, there are two splice variants of D2, termed D2S and D2L (Giros et al., 1993; Monsma et al., 1989). The D2L isoform has an additional 29 amino acids in the third intracellular loop, which confers distinct functional properties (Centonze et al., 2003; Usiello et al., 2000). D2S receptors are expressed primarily in presynaptic neurons and are involved in autoreceptor function, whereas D2L are expressed postsynaptically (De Mei et al., 2009; Usiello et al., 2000). Antipsychotics, especially FGA (Xu et al., 2002), show preferential binding to the postsynaptic D2L isoform (Usiello et al., 2000) and (**Table 1**). Translating this into human treatments, it may be proposed that the D2 "reserve" in humans is mainly composed of presynaptic D2S during antipsychotic treatment based on three key points. First, antipsychotics are prescribed at doses to achieve to 60-80% occupancy only (Kapur

and Seeman, 2001), enabling 20-40% of unbound free D2 receptors to bind endogenous dopamine. Second, as antipsychotics preferentially bind D2L (Usiello et al., 2000), a large proportion of the unbound free D2 receptors would be predicted to consist of the D2S isoform. Third, all other dopamine receptors (D1, D3, D4, D5), for which antipsychotics have some binding affinity (**Figure 1**), would be partially blocked. As a consequence, the long-lasting increase in endogenous dopamine levels following the initial antipsychotic treatment period would bind preferentially to the D2S "reserve", for which dopamine has higher affinity and potency than for other dopamine receptors (Aihara et al., 2004; Beaulieu and Gainetdinov, 2011). This hypothetical mechanism is depicted in **Figure 2**. Presynaptic D2S receptors couple to the inhibitory subtype of G-protein (Giros et al., 1989; Monsma et al., 1989). When the receptor is stimulated by endogenous dopamine, this provides an important negative feedback mechanism (Carlsson and Lindqvist, 1963) that controls neuronal firing (Lane and Blaha, 1986; Mercuri et al., 1985) and the synthesis and release of dopamine (Chesselet, 1984). The activation of this dopamine-driven auto-inhibition (Benoit-Marand et al., 2001; Suaud-Chagny et al., 1991) results in decreased behavioural activity with dimensional relevance to positive symptoms of schizophrenia in animals (Amato et al., 2006; Amato et al., 2008; Lomanowska et al., 2004) and therefore speculatively, decreased positive symptoms of psychosis in humans. From this theoretical standpoint, dopamine itself underlies not only psychosis onset in schizophrenia, but also, the therapeutic effect of antipsychotic drugs. This mechanism may also provide a mechanism underlying recurrent active and residual psychotic episodes.

Although this suggested antipsychotic role played by dopamine itself appears counterintuitive, it is interesting to note that patients with schizophrenia often abuse substances that stimulate dopamine release such as nicotine and/or other psychostimulants (de Leon and Diaz, 2005; Volkow, 2009). The neurobiological causes of these co-morbid

behaviours are not understood, although epigenetic susceptibility has been implicated (Tsankova et al., 2007). However, it could be argued that the mild effect of these addictive substances on dopamine release, co-administered with antipsychotics may help to prolong initial antipsychotic efficacy according to the above-described mechanism. After all, it is unlikely that patients use psychostimulants to induce psychosis.

An indirectly related but supportive observation comes from the proposal to treat Parkinson's symptoms using haloperidol or other D2 antagonists, an idea that was patented by Professor Philipp Seeman in 2010 (Patent N. CA2769149 A1). It is explained that a mild dopamine supersensitivity induced by treatment with antipsychotics may alleviate Parkinson's symptoms. The underlying mechanism of this therapy would be similar to the placebo effect mechanism observed in Parkinson's (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez et al., 2002; Lidstone et al., 2010), described in point #10. Thus, the increase in extracellular dopamine consequent to the initial haloperidol treatment would activate the reward system via stimulation of D2/3 receptors and reduce Parkinson's symptoms to some extent.

Concerns regarding D2 receptor agonism vs. antagonism

The onset of antipsychotic efficacy is observed within 24 hours after treatment and is not delayed (or subordinated) by the onset of long-term dependent processes. It is rather associated with the accumulation of extracellular dopamine in striatal synapses leading to an auto-inhibition mechanism. Long-term antipsychotic treatment efficacy decreases despite sufficient D2 blockade due to the fact that blocking D2 receptors may not be the only mechanism by which antipsychotics function. Although antipsychotics bind D2 receptors, we propose here a novel hypothesis that the antipsychotic effect is based on an indirect

stimulation of presynaptic D2 autoreceptors. Thus, the time course of antipsychotic treatment failure may in fact be dependent on elimination kinetics of extracellular dopamine in the synapse rather than the duration of D2 receptor occupancy. An indirect agonism mediated by antipsychotics would further support the development of dopamine supersensitivity. In the hypothetical condition of a sustained indirect presynaptic dopamine agonism and of a direct postsynaptic antagonism driven by antipsychotics, it follows that presynaptic receptors would be decreased (desensitization (Lomanowska et al., 2004; Zhang et al., 1994) while post-synaptic receptors would increase (sensitization (Seeman et al., 2005). Thus, any condition triggering the release of dopamine in patients would necessarily stimulate the available post-synaptic receptors, causing behavioural supersensitivity, which would facilitate the occurrence of relapse. The milder neurobehavioral supersensitivity induced by SGA may be due to their ability to control dopamine release indirectly via a combination of agonism/antagonism of the serotoninergic 5-HT1A and 5-HT2A-C receptors (De Deurwaerdere and Spampinato, 1999; Dewey et al., 1995; Ichikawa and Meltzer, 2000; Ugedo et al., 1989). As SGA mostly bypass the long-lasting postsynaptic D2 blockade, little or no dopamine supersensitivity would be predicted to occur with these drugs. Furthermore, new antipsychotics agents, such as aripiprazole explicate their effects through partial agonism at dopamine D2 receptors.

As already mentioned, 20-30% of patients with schizophrenia targeted with a significant D2 occupancy will never respond to D2 antipsychotic blockade. Adhering to the present proposal, an antipsychotic efficacy cannot be seen solely with dopamine receptor antagonism. If this hypothesis is correct, for an antipsychotic to be effective, especially in ameliorating positive symptoms, a substantial level of extracellular dopamine is required in order to stimulate D2S. Therefore, non-responder patients may express reduced levels of D2S. Alternatively, non-responders may have disrupted dopamine synthesis, release or

uptake, preventing the common rise of extracellular dopamine seen upon D2 blockade. This possibility would for example support previous evidences showing “normal” dopamine synthesis capacity in treatment resistance patients. Clozapine has longer-term efficacy than other antipsychotics; it is often effective in non-responder patients and has reduced risk to induce dopamine supersensitivity. Its combined ability to stimulate and antagonize 5-HT1 and 5-HT2A respectively along with its mild blocking action on D2 and other dopamine receptors may result in either stimulating D2S directly and/or inhibiting dopamine release via 5-HT receptors. Therefore, as clozapine controls dopamine, bypassing a significant D2 blockade, it does not induce adaptation processes leading to a significant D2S desensitization and/or D2L sensitization.

Aripiprazole is clinically effective despite not being an antagonist of D2 receptors. In light of the present proposal both FGA and SGA work as partial (indirect) agonists, displaying a similar mechanism to aripiprazole.

Antipsychotics are more effective in the presence of moderately high levels of extracellular dopamine, whether it is endogenous or pharmacologically-induced. Higher synaptic dopamine levels would help antipsychotics increase endogenous dopamine in order to reach a greater number of available D2S receptors.

Placebo treatment may reproduce a consistent antipsychotic effect in patients with schizophrenia due to the effects of reward expectation on the dopaminergic system, as observed in the seminal experiment of Dr. Shultz (Schultz, 1998). Likewise, the expectation to receive a medication from a doctor may be perceived as a positive reward by patients. This condition by itself can be sufficient to stimulate dopamine release in a similar fashion as observed in the treatment of Parkinson’s patients (de la Fuente-Fernandez et al., 2001). Therefore, we suggest here that, based on our hypothesis, moderate release of dopamine,

such as that induced by placebo, would stimulate the D2S receptors, for which dopamine has higher affinity than for D2L, leading to a degree of antipsychotic response in patients.

Limitations of 'dopamine, the antipsychotic molecule' hypothesis

According to our proposal, antipsychotics may work better in the presence of moderately high levels of extracellular dopamine, because tonic synaptic dopamine levels would facilitate the role of antipsychotics to indirectly stimulate the presynaptic D2S reserve. Thus, the occupancy of most dopamine receptors (with the exception of a proportion of D2S) by antipsychotics would shift the endogenous dopamine towards binding available D2S. Despite the fact that such an indirect mechanism may occur, we acknowledge that at present it is difficult to distinguish between D2S and D2L binding *in vivo* and it is even more ambitious to verify that dopamine is selectively binding a proportion of available D2S while antipsychotics are selectively occupying the rest of dopamine receptors. However, we are currently conducting preclinical experiments in order to verify this hypothesis.

Another limitation of the present interpretation is based on the exclusive focus on the two D2 receptor isoforms. In fact, as described previously the D2 receptors are expressed pre – and post-synaptically in heterogeneous types of neurons (dopaminergic, GABAergic MSNs and cholinergic neurons) and depending on which of these receptors is altered in affected patients, antipsychotic therapy could produce distinctive effects (such the condition listed previously). A second and related source of variability may instead be based on the fact that many D2-expressing neurons co-release multiple neurotransmitters (i.e. dopamine, glutamate, GABA and noradrenaline). Thus, the final outcome of antipsychotic treatment could be linked with the antipsychotic-mediated blockade of a particular neurotransmitter or combination of neurotransmitters. Accordingly, antipsychotics can modulate other

monoamines resulting in the release of serotonin (Amato et al., 2011b; Amato, 2015; Amato et al., 2016a) or inhibition of noradrenaline neurotransmission (Amato et al., 2011a). Finally, D2 receptors also contribute to glutamate release in the striatopallidal pathway (Ciranna, 2006).

Conclusion

Here we suggest a number of mechanisms that may underlie the extreme and still unpredictable variability in behavioural and clinical responses to antipsychotic medications (side effects as well as therapeutic effects). In particular we have focused on the possibility that the efficacy of antipsychotic drugs can be mediated by an indirect stimulation of presynaptic D2 receptors, at least for positive symptoms of schizophrenia. The increased release of endogenous striatal dopamine consequent to antipsychotic treatment will bind a dopamine D2 receptor reserve. The D2 receptor reserve is defined herein as the difference between the total number of available D2 receptors (100%) and the proportion of D2 receptors that are bound by an antipsychotic drug when given at a dose that achieves the antipsychotic therapeutic window (60-80% blockade of central D2 receptors). The D2 receptor reserve therefore comprises the unbound fraction of D2 receptors, within a range of 40 to 20% of the total D2 receptor population, depending on the dose of antipsychotic given. The receptor reserve is mostly formed by D2S, which is located presynaptically and inhibits synthesis and release of dopamine when stimulated. Therefore, the ability of antipsychotics to indirectly stimulate the presynaptic D2 receptor reserve combined with a postsynaptic dopamine receptor blockade would allow endogenous dopamine to produce an antipsychotic effect. Our novel interpretation is hypothetical and there are key aspects that await experimental verification, which serves as the basis of our on-going work. Nevertheless, it has the potential to bridge the mechanistic gap between FGA and the

newest compounds, and to extend our own mechanistic understanding beyond the blockade of dopamine D2 receptors (de Bartolomeis et al., 2015).

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Table and Figure legends

Table 1 *Averaged values obtained from the National Institute of Mental Health Psychoactive Drug Screening Program database (http://pdsp.med.unc.edu).

Figure 1 Averaged values obtained from (Bymaster et al., 1996; Schotte et al., 1996) (Richtand et al., 2007) and from the National Institute of Mental Health Psychoactive Drug Screening Program database (http://pdsp.med.unc.edu).

Figure 2 A. Antipsychotics and dopamine binding to dopamine receptors of striatal neurons. **B.** Magnification of a striatal synapse showing that therapeutic antipsychotic dosing may prevalently

block postsynaptic D2L (long-isoform) receptors. The increased extracellular dopamine stimulated by antipsychotics would instead stimulate presynaptic D2S (short-isoform) receptors.

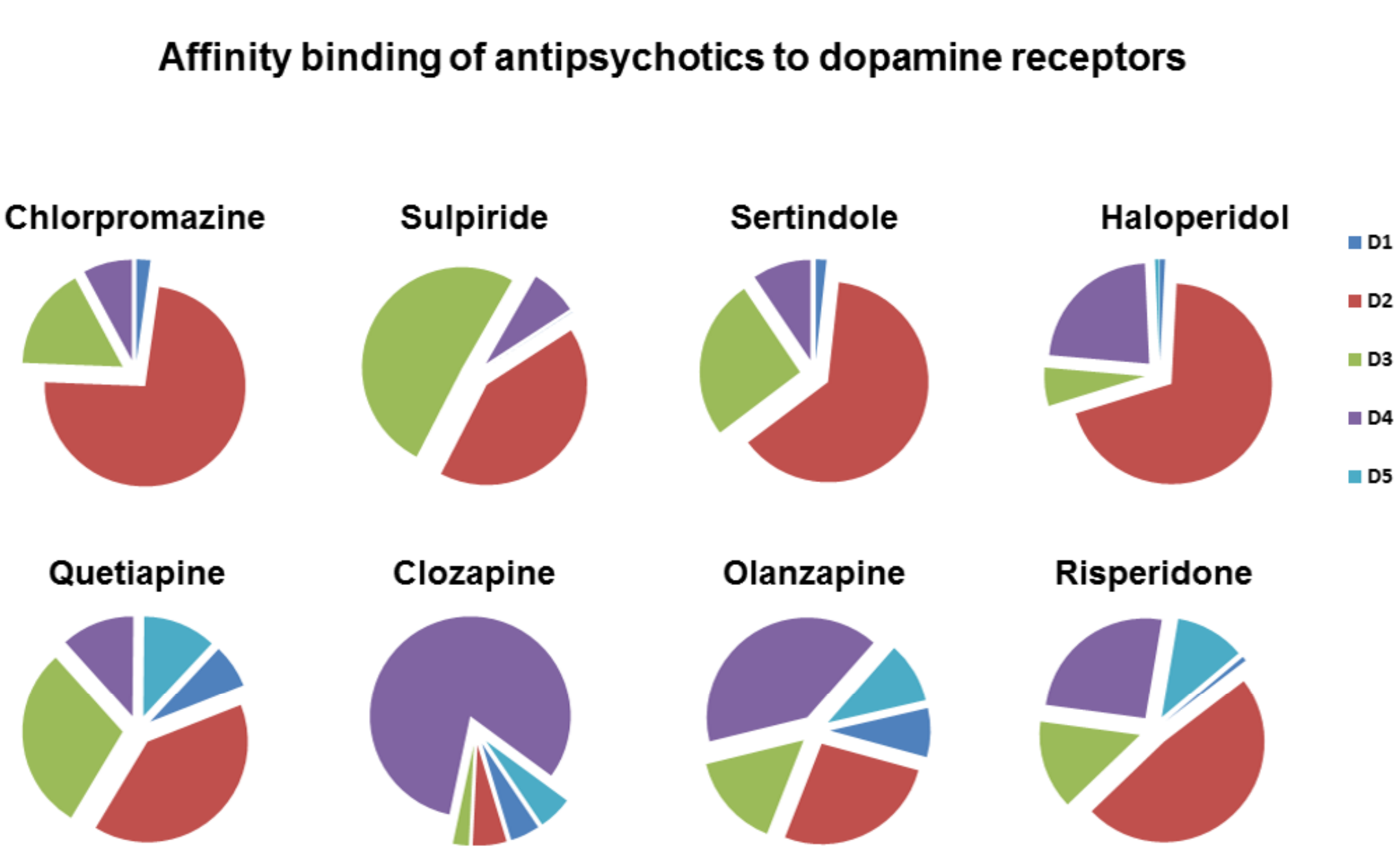
Affinity binding of antipsychotics to dopamine receptors
Chlorpromazine
Sulpiride
Sertindole
Haloperidol
D1
D2
D3
D4
D5
Quetiapine
Clozapine
Olanzapine
Risperidone

Figure 1

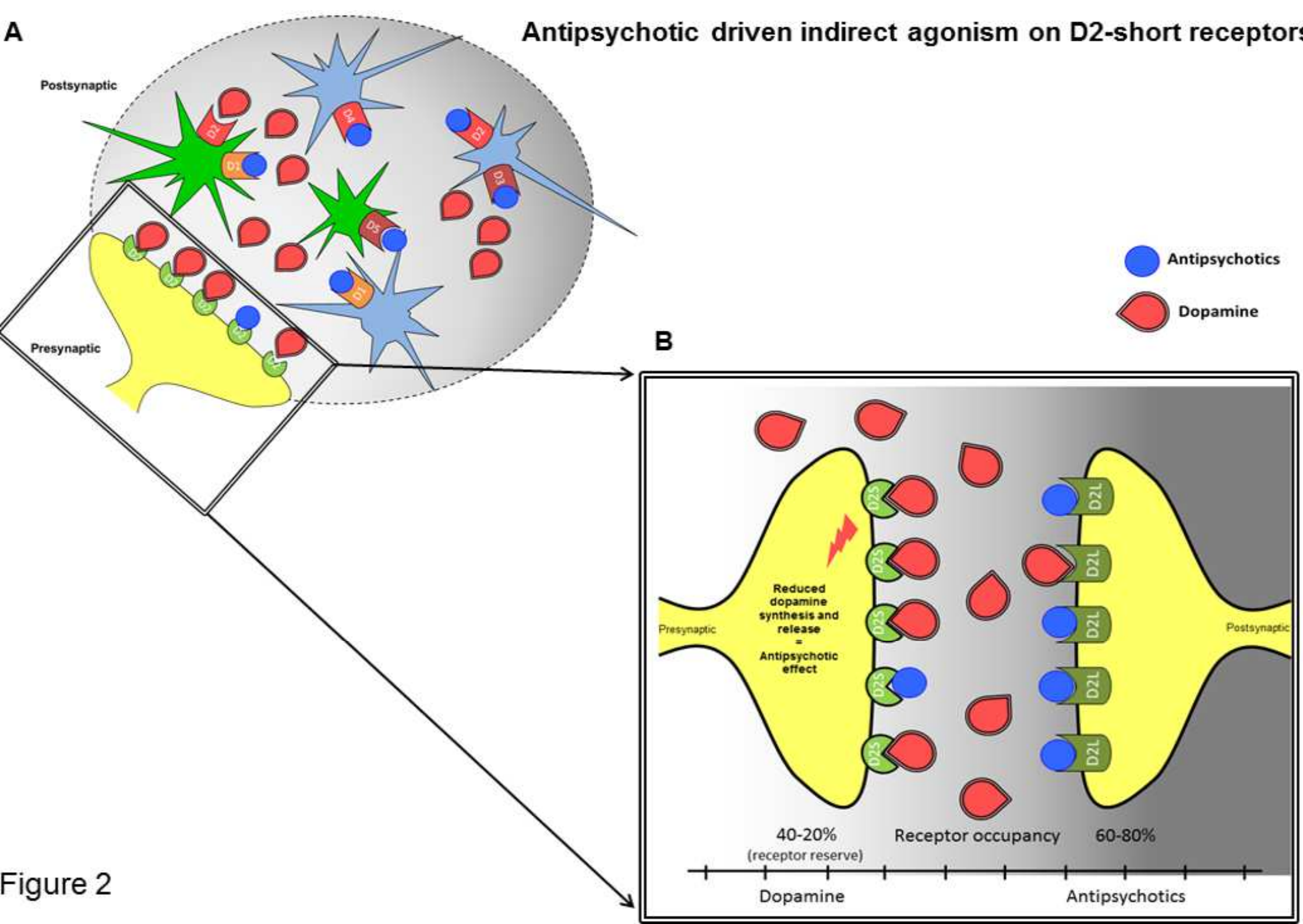
A
Antipsychotic driven indirect agonism on D2-short receptors
Postsynaptic
Presynaptic
D1
D2
D3
D4
D5
Antipsychotics
Dopamine
B
Presynaptic
Reduced dopamine synthesis and release = Antipsychotic effect
D2S
D2L
Postsynaptic
40-20%
(receptor reserve)
Receptor occupancy
60-80%
Dopamine
Antipsychotics

Figure 2

Affinity binding of antipsychotics to dopamine D2 receptor isoforms

Antipsychotics	Dopamine D2 receptor isoforms affinity binding (Ki)*	
	D2-long	D2-short
Haloperidol	1.53	8.75
Chlorpromazine	2.52	29
Clozapine	185.25	464.5
Sertindole	3.81	5.8
Olanzapine	34.35	40.38
Risperidone	4.16	4.73
Sulpiride	287	177.5
Quetiapine	702	465.8

Table 1